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SERUM TOTAL CHOLESTEROL AND CANCER MORTALITY IN A POPULATION-BASED COHORT OF FINNISH MEN

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Syöpäkasvaimien poikkeava lipidiaineenvaihdunta on todettu sekä in vitro -tutkimuksissa syöpäsoluissa että epidemiologisissa tutkimuksissa syöpäpotilaiden poikkeavana lipidiprofiilina. Useissa epidemiologisissa töissä matala kokonaiskolesteroli, HDL-kolesteroli ja LDL-kolesteroli ovat lisänneet syövän riskiä. Useita aiempia tutkimuksia kuitenkin rajoittaa lyhyt seuranta-aika, joidenkin lipidikomponenttien puuttuminen tai kolesterolin mittauskertojen vähyys. Tämän tutkimuksen tavoitteena oli tutkia seerumin lipidiprofiilin yhteyttä syöpäkuolemaan retrospektiivisessä kohorttitutkimuksessa. Tutkimme myös statiinien käytön aikana tapahtuneen kolesterolitason laskun yhteyttä syöpäkuolleisuuteen tutkiaksemme mahdollisen syy-yhteyden suuntaa.

Muodostimme tutkimuskohortin 80,458 Finnish Randomized study of Screening for Prostate Cancer (FinRSPC) -tutkimukseen vuosina 1996-1999 osallistuneiden miesten pohjalta. Yhdistimme kohortin Fimlabin tietokantaan jolloin löysimme 16,924 miestä, joilta oli mitattu kokonaiskolesteroli vähintään kerran. Jaoimme miehet, joilla oli vähintään yksi lipidimittaus jonakin vuonna, korkean ja matalan kolesterolin ryhmään käyttäen hyperkolesterolemian kliinisiä raja-arvoja. Laskimme riskitiheyssuhteet (hazard ratio, HR) ja 95% luottamusvälit (95% CI) Coxin regressiometodia käyttäen sekä syöpäkuolemalle ylipäänsä, että kuolemalle eniten syöpäkuolemia aiheuttaviin syöpiin erikseen tarkasteltuna. Pitkän aikavälin yhteyttä tutkimme lag time -analyysilla. Käsittelimme seerumin lipidiparametreja aikariippuvaisina muuttujina. Suoritimme alaryhmäanalyyseja tutkiaksemme painoindeksin, lääkkeiden käytön, oheissairastavuuden sekä kolesterolimittausten lukumäärän vaikutusta lipidiprofiilin ja syöpäkuoleman yhteyteen.

Matala kokonaiskolesteroli oli yhteydessä korkeampaan syöpäkuolleisuuteen. Vastaava yhteys todettiin myös matalan HDL-kolesterolin sekä matalan LDL-kolesterolin ja syöpäkuoleman riskin välillä. Triglyseridit eivät olleet tilastollisesti merkitsevällä tavalla yhteydessä syöpäkuoleman riskiin. Ajallista yhteyttä tutkivissa lag time -analyyseissä tämä yhteys oli havaittavissa 10 vuotta ennen syöpäkuolemaa kokonaiskolesterolin osalta, 3 vuotta ennen syöpäkuolemaa HDL-kolesterolin osalta ja 5 vuotta ennen syöpäkuolemaa LDL-kolesterolin osalta. Statiinien käytön aikana tapahtunut kolesterolitason lasku oli yhteydessä matalampaan syöpäkuoleman riskiin mutta löydös ei ollut tilastollisesti merkitsevä.

Sisällys

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ABSTRACT

Background

Aberrant lipid metabolism has been observed both in vivo in cancer cells as well as in epidemiological studies among cancer patients, but many of the studies have major limitations and there are discrepancies in the results.

Materials and methods

We estimated the long-term associations between serum total cholesterol, LDL, HDL and triglycerides and cancer mortality in a retrospective cohort study based on the 80,45 8 men identified for the Finnish Randomized study of Screening for Prostate Cancer (FinRSPC) during 1996-1999. Total cholesterol measurements were available for 16,924 men. Men with lipid measurements available on a given year were stratified into two groups based on clinical threshold values. Cox regression method was used to calculate hazard ratios and 95% confidence intervals for risk of cancer death overall and separately for death due to most commonly fatal cancer types. Serum lipid parameters were analyzed as a time-dependent variable. Subgroup analyses were performed to evaluate the effect of BMI, medication use, background comorbidities and number of cholesterol measurements on the risk association between cholesterol and other lipid parameters and cancer death. Long-term risk associations were evaluated in lag time analyses.

Results

There was an inverse association between total cholesterol and overall cancer mortality (HR 0.60, 95% CI 0.46-0.79). Similar inverse risk associations were observed also for HDL (HR 0.41, 95% CI 0.32-0.53) and LDL cholesterol (HR 0.53, 95% CI 0.39-0.72) but not for triglycerides (HR 1.10, 95% CI 0.85-1.42). The inverse association persisted up to 10 years lag time for total cholesterol, up to 3 years for HDL, and up to 5 years for LDL cholesterol measurements. Compared to those statin users whose serum total cholesterol did not decrease or increased during their use of statins, risk of cancer death was decreased for

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those whose serum total cholesterol decreased by 1.53 mmol/l or less (HR 0.76, CI95% 0.45-1.29) and for those whose serum total cholesterol decreased by more than 1.53 mmol/l (HR 0.82, CI95% 0.49-1.39), but the findings were not statistically significant.

Conclusion

Low serum total cholesterol is associated with cancer mortality for up to 10 years before cancer death, supporting reverse causation. Intervention with statins may lower the risk of cancer death, supporting hypercholesterolemia as a modifiable cancer risk factor.

1: INTRODUCTION

Lipids play an important part in cellular membrane structures, energy metabolism and signaling[1]. Aberrant energy metabolism is an established trait of cancer cells[2] and this may affect also lipid metabolism. Both de novo lipid synthesis[3] and exogenous lipid uptake[4] have been proposed as means for satisfying the high demand posed by fast proliferation. There is also evidence that membrane cholesterol is required in the formation of so-called lipid rafts, cell membrane microdomains which are mediators of survival signals essential to cancer cells[5].

Elevated serum total cholesterol is a well-established risk factor for cardiovascular disorders[1], but its' role as cancer risk factor is more controversial. The association between cancer and serum lipid concentrations has been studied quite extensively[6], but many of the studies are limited and there are discrepancies in the results. Even though most studies report an association between low plasma cholesterol and cancer[7–13], there are also studies that found no association[14,15] or a V-shaped association i.e. an association between both low and high serum cholesterol concentrations and cancer[16,17]. Some studies focusing on colorectal cancer reported a positive association between serum total cholesterol and cancer incidence[18,19]. In many studies the risk association disappeared when the first follow-

up years were excluded from the analysis, suggesting reverse causation due to spontaneously decreasing serum cholesterol due to undiagnosed advanced cancer[7–11], but there are other studies[12,13,20], in which the association between low cholesterol and cancer persisted even in the long-term. Reports of an association between use of cholesterol-lowering statin drugs and lowered cancer mortality compared to non-users further support the role of cholesterol in cancer etiology[21].

Many of the previous studies are limited by short follow-up or focusing only on total cholesterol, without comprehensive data on all lipid components and limited information on timing of cholesterol measurements in relation to cancer diagnosis and death. Also many of the studies relied on a single cholesterol measurement which makes it harder to determine the long-term associations as well as the nature of the possible causal relationship between serum cholesterol and cancer.

Because previous evidence on serum total cholesterol as a risk factor for cancer mortality is limited, we estimated the long-term associations between total cholesterol, serum LDL, HDL and triglycerides and cancer mortality in a population-based cohort of Finnish men.

2: MATERIALS AND METHODS

2.1: Study cohort

Our cohort is based on 80,458 men originally identified from the Finnish Population Register Centre for the Finnish Randomized study of Screening for Prostate Cancer (FinRSPC) during 1996-1999. The detailed study protocol has been described earlier[22]. The men were 55-67 years old at baseline. Prevalent cases of cancer were identified from the Finnish Cancer Registry and excluded. Follow-up started at the FinRSPC baseline in 1996-1999, and continued until death, emigration from Finland or 31 December 2015, whichever came first.

Information on causes of death was acquired from the death certificate registry of Statistics Finland. The data included immediate, primary and contributory causes of death recorded as ICD-10 codes. The registry covers reliably all deaths in Finland by mandatory documentation of causes of death. The present study included deaths until the end of 2015.
Cancer deaths were defined by ICD-10 codes C00-D48 recorded as the primary cause of death. Deaths by cancer type were defined by the following ICD-10 codes: lung cancer C34, colorectal cancer C18-C20, pancreatic cancer C25, stomach cancer C22, liver cancer C22, non-Hodgkin lymphoma C82, C83 or C85, kidney cancer C64, bladder cancer C67 and brain or CNS cancer C71 or C72.

Information on purchases of cholesterol-lowering, antidiabetic and antihypertensive drugs as well as on physician-prescribed purchases of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) during 1995-2015 was acquired by linking the cohort to national prescription database maintained by the Social Insurance Institution (SII) of Finland. The linkage was performed using personal identification number. SII provides reimbursements for physician-prescribed drug purchases. All Finnish citizens are entitled to the reimbursement. Each reimbursed purchase is registered by the prescription database. The registry does not cover drugs used during hospital inpatient periods.

To obtain information on co-morbidity diagnoses registered during 1995-2015 the study population was linked to the national Care Registry (HILMO) maintained by the National Institute for Health and Welfare. HILMO registers all diagnoses from in- and outpatient hospital contacts in all Finnish health care units. Diagnoses from the primary care are not recorded. Based on recorded diagnoses Charlson Comorbidity Index was calculated for each participant to reflect the likelihood of dying of co-morbidities.

A survey with questions about height and weight for calculation of BMI was mailed along with the third round FinRSPC screening invitations in 2004-2008. Response rate was 93%, and BMI was available for 11,698 men[23].

All linkages between data sources were carried out using unique personal identification number.

2.2: Information on serum cholesterol parameters

The study cohort was linked to Fimlab database which registers all laboratory results in the Pirkanmaa region. Fimlab is the primary distributor of medical laboratory services in the Pirkanmaa region. This way information was acquired on results of serum total cholesterol measurements (n=16,924 men with at least one measurement available), LDL (n=15,425), HDL (n=15,625) and triglyceride measurements (n=17,043).

Yearly mean of total cholesterol, LDL, HDL and triglycerides was calculated for each follow-up year using all values measured during a given year. Men with lipid measurements available on a given year were stratified into two groups based on clinical threshold values; total cholesterol level of 5.0 mmol/l, HDL level of 1.0 mmol/l, LDL level of 3.0 mmol/l and triglyceride level of 1.7 mmol/l. Men with no lipid measurements available on a given year were categorized into a separate category.

2.3: Statistical analysis

Cox regression method was used to calculate hazard ratios and 95% confidence intervals for risk of cancer death overall and separately for death due to most commonly fatal cancer types. Deaths due to prostate cancer were included in the overall cancer mortality, but prostate cancer-specific death will be analyzed in detail in a separate study. Timeline for the follow-up was in years and months since the FinRSPC baseline. Cox regression was adjusted for age and medication use (antidiabetic drugs, antihypertensive drugs, statins, anticoagulants, aspirin and other NSAIDs) and additionally for Charlson Comorbidity Index.

Serum lipid parameters were analyzed as time-dependent variable, i.e. the lipid level was updated for each follow-up year based on the average of the available yearly measurements.

Subgroup analyses were performed to evaluate the effect of BMI, medication use, background comorbidities and number of cholesterol measurements on the risk association between cholesterol and other lipid parameters and cancer death. Long-term risk associations were evaluated in lag time analyses where serum total cholesterol level was lagged forward in the follow-up time, i.e. cholesterol level measured in 2005 was analyzed on 2006 in 1-year lag time analysis. We performed separately 1-year, 3-year, 5-year, 10-year and 20-year lag time analyses.
The effect of excess mortality due to non-cancer causes on the risk association was explored using competing risks regression method described by Fine and Gray.

All statistical analyses were performed using IBM SPSS 23 statistical software, except the competing risks regression analyses which were performed using Stata.

3: RESULTS

3.1: Population characteristics

The population characteristics are reviewed in *table 1*. There were 16,924 men in our cohort with at least one serum total cholesterol measurement available, 15,625 men with at least

one HDL measurement; 15,425 with LDL available and 17,043 men with at least one triglyceride measurement. The median number of available total cholesterol measurements was seven. When divided into two subgroups by mean total cholesterol during follow-up, there were 10,301 men in the group with mean total cholesterol below the clinical recommendation of 5 mmol/l or lower and 6,623 in the group with mean total cholesterol above 5 mmol/l.

During the median follow-up of 17.2 years after baseline there were 1,430 (8.1% of the cohort) cancer deaths among the men with serum total cholesterol measurements available. Of these 858 (60.0% of all cancer deaths) occurred in the low total cholesterol group and 572 (40.0% of all cancer deaths) in the high total cholesterol group.

Age distribution at baseline was similar between the groups. Body mass index was 27.1 in the low total cholesterol group and 26.4 in the high total cholesterol group (p for difference < 0.001).

Use of statins, antihypertensive drugs, antidiabetic drugs, aspirin and NSAIDs was more prevalent in the low total cholesterol group, p for difference by total cholesterol level < 0.001 for each. The biggest difference was seen in the use of statin drugs; when taking into account all available cholesterol measurements, 5,493 (51.5%) men in the low total cholesterol group had used statins, while the number of users was 2586 (37.4%) men in the high total cholesterol group. When stratifying by baseline cholesterol level, the proportion of statin users in the low and high total cholesterol group was 42.8% and 48.4%, respectively (*Supplementary table 1*).

Median Charlson comorbidity index points were 1 for the low total cholesterol group and 0 for the high total cholesterol group. The median number of cholesterol measurements was 8 in the low total cholesterol group and 6 in the high total cholesterol group.

Table 1. Baseline characteristics of study population by mean cholesterol level during follow-up.

Cohort of participants in the Finnish Randomized Study of Prostate Cancer Screening between 1996-2014.

		Mean cholesterol during follow-up	
	Full cohort	5 mmol/l or below	Above 5 mmol/l
Participants with at least one serum total cholesterol measurement available (n)	16,924	10,301	6,623
Median (IQR) age at baseline (years)	59 (55-63)	59 (55-63)	59 (55-63)
Number of deaths	5,216	3,136	2,080
Median (IQR) follow-up time (years)	17.2 (14.2-19.0)	18.0 (16.8-19.0)	18.0 (15.7-19.0)
Median (IQR) body mass index (kg/m2)*	26.3 (24.3-29.0)	27.1 (24.9-29.9)	26.4 (24.3-29.1)
Median (IQR) number of measurements available	7 (3-12)	8 (4-13)	6 (3-11)
Median (IQR) Charlson Co-morbidity Index	1 (0-2)	1 (0-2)	0 (0-2)
Use of statin drugs; n (%)	8079 (46.0%)	5493 (51.5%)	2586 (37.4%)
Use of antihypertensive drugs; n (%)	12773 (72.7%)	8325 (78.1%)	4448 (64.4%)
Use of antidiabetic drugs; n (%)	3957 (22.5%)	2989 (28.0%)	968 (14.0%)
Use of aspirin; n (%)	3507 (20,0%)	2352 (22.1%)	1155 (16.7%)
Use of NSAID drugs; n (%)	14196 (80,8%)	8713 (81.7%)	5483 (79.4%)
Cause of death			
All cancers	1,430	858	572
Lung cancer	357	207	150
Colorectal cancer	143	88	55
Pancreatic cancer	112	70	42
Gastic cancer	56	33	23
Liver cancer	71	53	18
Non-Hodgkin lymphoma	48	32	16
Kidney cancer	40	25	15
Bladder cancer	39	24	15
Brain and CNS cancers	39	24	15

Available for 11,345 men (67.0% of the cohort)

Supplement table 1. Baseline characteristics of study population by baseline cholesterol level.

Cohort of participants in the Finnish Prostate Cancer Screening Trial between 1996-2014.

		Mean cholesterol during follow-up	
	Full cohort	5 mmol/l or below	Above 5 mmol/l
Participants (n)	16,924	8,134	9,562
Median (IQR) age at baseline (years)	59 (55-63)	59 (55-63)	59 (55-63)
Number of deaths	5,216	2,431	2,080
Median (IQR) follow-up time (years)	17.2 (14.2-19.0)	18.0 (16.3-19.0)	18.0 (16.6-19.0)
Median (IQR) body mass index (kg/m2)*	26.3 (24.3-29.0)	26.8 (24.7-29.4)	26.8 (24.7-29.6)
Median (IQR) number of measurements available	7 (3-12)	6 (3-11)	8 (4-13)
Median (IQR) Charlson Co-morbidity Index	1 (0-2)	1 (0-2)	1 (0-2)
Use of statin drugs; n (%)	8079 (46.0%)	5493 (42.8%)	2586 (48.4%)
Use of antihypertensive drugs; n (%)	12773 (72.7%)	8325 (73.7%)	4448 (71.7%)
Use of antidiabetic drugs; n (%)	3957 (22.5%)	2989 (24.7%)	968 (14.0%)
Use of aspirin; n (%)	3507 (20,0%)	2352 (19.3%)	1155 (20.3%)
Use of NSAID drugs; n (%)	14196 (80,8%)	8713 (80.4%)	5483 (80.8%)
Cause of death			
All cancers	1,432	708	724
Lung cancer	357	170	187
Colorectal cancer	143	70	73
Pancreatic cancer	112	61	51
Gastic cancer	56	28	28
Liver cancer	71	42	30
Non-Hodgkin lymphoma	48	29	19
Kidney cancer	40	21	19
Bladder cancer	39	24	15
Brain and CNS cancers	39	12	27

Available for 11,345 men (67.0% of the cohort)

3.2: Cancer mortality by serum total cholesterol and lipid fractions

There was an inverse association between total cholesterol and overall cancer mortality (HR 0.60, 95% CI 0.46-0.79). Similar inverse risk associations were observed also for HDL (HR 0.41, 95% CI 0.32-0.53) and LDL (HR 0.53, 95% CI 0.39-0.72) cholesterol but not for triglycerides (HR 1.10, 95% CI 0.85-1.42) *(Table 2)*.

In lag time analyses the inverse association remained up to 10 years lag time for total cholesterol, 3 years for HDL, and 5 years for LDL cholesterol measurements. In longer-term lag time analyses the risk estimates tended to rise for total cholesterol, up to HR 1.68 (95% CI 0.75-3.80) in the 20-year lag time analysis. A similar trend of rising risk estimates was seen also for HDL cholesterol. For LDL cholesterol and triglycerides, a similar rise in risk estimates was observed, albeit not as consistent. Interestingly, even though the main analysis did not show a significant association between triglyceride levels and cancer mortality, marginally non-significant positive associations between high triglyceride levels and cancer mortality were observed in the long-term analyses.

Similar inverse association disappearing with time were also observed when analyzing individual cancer types for total cholesterol, HDL and LDL in relation to cancer mortality. There was no substantial variation in the association patterns depending on the cancer type.

Lung cancer death displayed an inverse association with total cholesterol that persisted up to five years in the lag time analysis and an inverse association with LDL cholesterol up to 3 years in the lag time analysis (*table 3*). There was no statistically significant association between lung cancer death and HDL cholesterol or triglycerides.

Colorectal cancer death was not significantly associated with total cholesterol or LDL (*table 3*). There was an inverse association between HDL cholesterol and colorectal cancer death persisting up to 1 year in the lag time analysis. High triglyceride levels were statistically significantly associated with colorectal cancer death, but the finding disappeared in 1-year lag time analysis.

Pancreatic cancer showed an inverse association with HDL cholesterol (*table 3*). The association persisted up to 3 years in the lag time analysis. Other lipid fractions did not display statistically significant associations with pancreatic cancer death.

Of the less common cancer types (*supplement table 2*) risk of liver cancer death displayed an inverse association with cholesterol, LDL cholesterol and HDL cholesterol but no statistically significant association with triglycerides. The association with total cholesterol and LDL cholesterol for liver cancer death was only observed in the lag time analyses; the association with total

cholesterol persisted up to 3 years and the association with LDL cholesterol up to 1 year. The association with HDL persisted up to 1 year.

Non-Hodgkin lymphoma and bladder cancer showed inverse associations with HDL cholesterol levels that disappeared in the 3-year lag time analysis for non-Hodgkin lymphoma and 1-year lag-time analysis for bladder cancer. In kidney cancer, a consistently rising positive association was observed with triglyceride levels, but it was statistically significant only in the 10-year lag time analysis. Mortality from stomach cancer and cancers of the brain and central nervous system were not associated with any of the lipid fractions with statistical significance.

Table 2. Serum total cholesterol and lipid fraction levels and risk of all-cancer death.

		Lag time					
		Main analysis	1yr	3yrs	5 yrs	10yr	20yr
	N of deaths	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Serum cholesterol (mmol/l)							
5 or lower	858	Ref	Ref	Ref	Ref	Ref	Ref
above 5	572	0.60 (0.46-0.79)	0.68 (0.57-0.82)	0.75 (0.63-0.89)	0.73 (0.61-0.88)	0.74 (0.56-0.96)	1.68 (0.75-3.80)
LDL cholesterol (mmol/l)							
3 or lower	785	Ref	Ref	Ref	Ref	N/A	N/A
above 3	314	0.53 (0.39-0.72)	0.64 (0.52-0.79)	0.76 (0.63-0.93)	0.70 (0.55-0.88)		
Triglycerides							
1.7 or lower	1067	Ref	Ref	Ref	Ref	Ref	Ref
above 1.7	391	1.10 (0.85-1.42)	1.19 (0.99-1.44)	1.19 (0.99-1.42)	1.17 (0.96-1.42)	1.22 (0.92-1.61)	1.35 (0.75-2.42)
HDL cholesterol							
1.0 or lower	271	Ref	Ref	Ref	Ref	N/A	N/A
above 1.0	869	0.41 (0.32-0.53)	0.64 (0.53-0.78)	0.69 (0.56-0.85)	0.88 (0.69-1.14)		

Table 3. Serum total cholesterol and lipid fraction levels and risk of cancer death by the most common cancer types.

		Lag time					
		Main analysis	1yr	3yr	5yr	10yr	20yr
	N of deaths (non-exposed/exposed*)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Lung cancer deaths:							
Total cholesterol	207/150	0.64 (0.38-1.09)	0.63 (0.44-0.91)	0.64 (0.37-0.78)	0.59 (0.40-0.87)	0.63 (0.36-1.13)	0.81 (0.16-4.19)
LDL	192/79	0.52 (0.28-0.98)	0.52 (0.34-0.79)	0.52 (0.34-0.80)	0.75 (0.47-1.20)	N/A	N/A
HDL	53/225	0.85 (0.46-1.57)	0.72 (0.48-1.07)	0.92 (0.59-1.45)	1.20 (0.67-2.17)	N/A	N/A
Triglycerides	267/91	0.82 (0.46-1.46)	1.06 (0.72-1.54)	1.23 (0.86-1.79)	0.88 (0.57-1.36)	1.43 (0.80-2.58)	2.37 (0.59-9.49)
Colorectal cancer deaths:							
Total cholesterol	88/55	0.74 (0.29-1.89)	0.72 (0.38-1.35)	0.57 (0.32-1.00)	0.68 (0.39-1.18)	0.99 (0.45-2.22)	1.47 (0.16-13.13)
LDL	85/26	0.82 (0.29-2.30)	0.61 (0.30-1.24)	0.62 (0.33-1.17)	0.73 (0.36-1.45)	N/A	N/A
HDL	30/84	0.29 (0.11-0.73)	0.50 (0.26-0.96)	0.84 (0.44-1.63)	0.76 (0.36-1.59)	N/A	N/A
Triglycerides	111/37	2.18 (1.01-4.74)	1.54 (0.83-2.86)	0.94 (0.51-1.72)	0.77 (0.40-1.48)	0.35 (0.10-1.17)	0.78 (0.13-4.68)
Pancreatic cancer deaths:							
Total cholesterol	70/42	0.83 (0.35-1.99)	0.60 (0.33-1.12)	0.71 (0.39-1.30)	0.75 (0.38-1.45)	2.25 (0.88-5.75)	1.06 (0.11-10.17)
LDL	62/24	0.95 (0.36-2.47)	0.99 (0.54-1.82)	0.55 (0.27-1.16)	1.00 (0.45-2.20)	N/A	N/A
HDL	20/68	0.29 (0.12-0.69)	0.44 (0.24-0.81)	0.45 (0.24-0.85)	1.33 (0.46-3.81)	N/A	N/A
Triglycerides	87/28	0.85 (0.32-2.25)	0.81 (0.41-1.61)	1.00 (0.52-1.90)	1.13 (0.56-2.27)	1.54 (0.68-3.46)	1.09 (0.15-7.74)

* Low cholesterol values/high cholesterol values

Supplement table 2. Serum total cholesterol and lipid fraction levels and risk of cancer death by less common cancer types

		Lag time					
		Main analysis	1yr	3yr	5yr	10yr	20yr
	N of deaths (non-exposed/exposed*)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Stomach cancer deaths:							
Total cholesterol	33/23	0.63 (0.20-1.94)	1.98 (0.87-4.50)	1.12 (0.50-2.53)	0.60 (0.21-1.69)	1.03 (0.23-4.60)	N/A
LDL	25/11	0.59 (0.16-2.16)	0.81 (0.29-2.31)	0.95 (0.36-2.52)	0.32 (0.07-1.43)	N/A	N/A
HDL	7/29	0.70 (0.19-2.54)	0.92 (0.26-3.21)	0.95 (0.28-3.29)	2.46 (0.32-18.84)	N/A	N/A
Triglycerides	47/12	0.57 (0.13-2.49)	0.88 (0.30-2.61)	0.16 (0.02-1.16)	0.45 (0.10-1.98)	0.60 (0.07-5.38)	2.57 (0.23-28.40)
Liver cancer deaths:							
Total cholesterol	53/18	0.76 (0.25-2.37)	0.39 (0.16-0.92)	0.32 (0.12-0.83)	0.47 (0.21-1.04)	1.00 (0.34-2.97)	0.17 (0.02-1.88)
LDL	40/10	0.27 (0.03-2.15)	0.33 (0.12-0.93)	0.56 (0.21-1.50)	0.32 (0.10-1.07)	N/A	N/A
HDL	20/34	0.09 (0.02-0.32)	0.47 (0.24-0.95)	0.61 (0.25-1.46)	0.60 (0.25-1.45)	N/A	N/A
Triglycerides	44/29	1.79 (0.66-4.84)	1.11 (0.54-2.28)	1.14 (0.53-2.47)	1.60 (0.81-3.20)	0.60 (0.17-2.19)	0.53 (0.05-5.85)
Non-Hodgkin lymphoma deaths:							
Total cholesterol	32/16	0.46 (0.10-2.09)	0.34 (0.10-1.17)	0.20 (0.05-0.85)	0.22 (0.05-0.99)	0.18 (0.02-1.54)	N/A
LDL	33/5	N/A	0.12 (0.02-0.87)	0.29 (0.07-1.25)	N/A	N/A	N/A
HDL	14/27	0.07 (0.01-0.32)	0.29 (0.12-0.68)	0.59 (0.21-1.65)	0.58 (0.18-1.82)	N/A	N/A
Triglycerides	34/13	1.63 (0.51-5.21)	0.64 (0.19-2.18)	0.19 (0.03-1.44)	2.41 (0.92-6.36)	0.51 (0.06-4.34)	0.60 (0.06-6.65)

Kidney cancer deaths:							
Total cholesterol	25/15	0.72 (0.15-3.57)	0.63 (0.17-2.31)	0.37 (0.11-1.27)	0.72 (0.19-2.80)	1.67 (0.42-6.67)	N/A
LDL	22/11	0.88 (0.17-4.55)	0.73 (0.20-2.70)	0.56 (0.16-2.02)	0.85 (0.17-4.41)	N/A	N/A
HDL	9/25	0.59 (0.11-3.05)	1.08 (0.24-4.95)	0.37 (0.12-1.10)	1.21 (0.15-10.03)	N/A	N/A
Triglycerides	31/11	0.56 (0.07-4.55)	1.32 (0.36-4.89)	1.62 (0.57-4.61)	3.43 (0.99-11.88)	4.85 (1.21-19.41)	N/A
Bladder cancer deaths:							
Total cholesterol	24/15	1.15 (0.29-4.62)	0.56 (0.19-1.67)	0.52 (0.14-1.89)	1.24 (0.39-3.92)	2.61 (0.53-12.97)	N/A
LDL	22/12	0.64 (0.13-3.08)	0.73 (0.24-2.28)	2.09 (0.67-6.51)	0.92 (0.24-3.57)	N/A	N/A
HDL	4/30	0.19 (0.05-0.72)	0.71 (0.23-2.18)	2.51 (0.33-19.32)	N/A	N/A	N/A
Triglycerides	30/8	1.15 (0.24-5.37)	1.46 (0.53-4.06)	1.06 (0.30-3.81)	1.15 (0.31-4.25)	1.51 (0.36-6.35)	N/A
Brain and CNS cancer deaths:							
Total cholesterol	24/15	0.33 (0.07-1.47)	0.46 (0.17-1.23)	1.79 (0.69-4.65)	1.85 (0.69-4.99)	1.52 (0.14-16.77)	N/A
LDL	20/11	0.38 (0.08-1.74)	0.46 (0.15-1.37)	2.38 (0.88-6.42)	1.59 (0.53-4.74)	N/A	N/A
HDL	3/30	0.62 (0.17-2.31)	1.97 (0.46-8.46)	3.02 (0.40-22.82)	1.06 (0.23-4.78)	N/A	N/A
Triglycerides	33/6	0.72 (0.16-3.27)	0.81 (0.28-2.38)	0.83 (0.24-2.90)	1.15 (0.37-3.59)	4.94 (0.45-54.58)	N/A

* Low cholesterol values/high cholesterol values

3.3: Cancer mortality by changes in cholesterol level after initiation of statin use

Compared to those statin users whose serum total cholesterol did not decrease or increased after the first statin purchase, risk of cancer death was non-significantly decreased among those whose serum total cholesterol decreased by 1.53 mmol/l or less (HR 0.76, CI95% 0.45-1.29) and for those whose serum total cholesterol decreased by more than 1.53 mmol/l (HR 0.82, CI95% 0.49-1.39) *(table 4)*. Similar associations were not observed for decreases in LDL cholesterol or triglycerides during statin use.

Table 4. Change in serum cholesterol after initiation of statin treatment and cancer mortality.

	Change in Total cholesterol			Change in LDL			Change in Triglycerides		
	None or increased	Decrease by 1.52 mmol/l or less	Decreased more than 1.52 mmol/l	None or increased	Decrease by 0.96 mmol/l or less	Decreased more than 0.96 mmol/l	None or increased	Decrease by 0.30 mmol/l or less	Decreased more than 0.30 mmol/l
Risk of cancer death									
HR (95% CI)	Ref	0.76 (0.45-1.29)	0.82 (0.49-1.39)	Ref	0.95 (0.43-2.09)	1.55 (0.75-3.21)	Ref	0.96 (0.69-1.33)	1.00 (0.76-1.33)
N of cancer deaths	155	130	17	51	23	9	157	78	75

3.4: Subgroup analyses

There was no clear effect modification by BMI, statin use or number of available cholesterol measurements (*table 4)*.

Subgroup analysis by Charlson comorbidity index (*table 4*) showed no effect modification for total cholesterol, LDL or triglyceride levels. An exception was HDL cholesterol; those with no co-morbidities displayed an inverse association between HDL levels and cancer mortality (HR 0.14, CI95% 0.05-0.37) while among men with most co-morbidities (Charlson Index 3 points or more) displayed a weaker risk association (HR 0.67, CI95% 0.46-0.96), p for interaction = 0.001.

Table 4: subgroup analysis by BMI, statin use, number of serum total cholesterol measurements and Charlson comorbidity index.

		Subgroup analysis by BMI			Subgroup analysis by statin use	
		BMI 26.3 or lower	BMI over 26.3		No statin use	Statin use
	N of deaths (low BMI/high BMI)	HR (95% CI)	HR (95% CI)	N of deaths (no statin use/ statin use)	HR (95% CI)	HR (95% CI)
Serum cholesterol (mmol/l)						
5 or lower	49/57	Ref	Ref	482/376	Ref	Ref
above 5	31/36	0.34 (0.04-2.62)	1.04 (0.44-2.47)	347/225	0.57 (0.41-0.81)	0.64 (0.41-1.00)
LDL cholesterol (mmol/l)						
3 or lower	48/60	Ref	Ref	381/404	Ref	Ref
above 3	22/25	0.38 (0.05-3.03)	0.33 (0.10-1.10)	198/116	0.49 (0.33-0.72)	0.52 (0.31-0.90)
Triglycerides (mmol/l)						
1.7 or lower	70/63	Ref	Ref	667/400	Ref	Ref
above 1.7	10/30	4.16 (1.25-13.82)	0.76 (0.29-2.01)	184/207	1.27 (0.88-1.83)	1.04 (0.72-1.49)
HDL cholesterol (mmol/l)						
1.0 or lower	7/23	Ref	Ref	667/120	Ref	Ref
above 1.0	63/62	1.03 (0.13-8.23)	0.98 (0.39-2.45)	184/412	0.30 (0.21-0.43)	0.53 (0.37-0.76)
	Subgroup analysis by number of available measurements			Subgroup analysis by Charlson comorbidity index		
	N of deaths (7 or less/more than 7)	HR (95% CI)	HR (95% CI)	N of deaths (0/1-2/3 points)	HR (95% CI)	HR (95% CI) HR (95% CI)

5 or lower	621/237	Ref	Ref	44/343/471	Ref	Ref	Ref
above 5	452/120	0.60 (0.43-0.82)	0.81 (0.50-1.31)	36/242/294	0.41 (0.15-1.11)	0.51 (0.34-0.75)	0.75 (0.51-1.12)
LDL cholesterol (mmol/l)							
3 or lower	515/270	Ref	Ref	42/265/478	Ref	Ref	Ref
above 3	239/75	0.41 (0.28-0.62)	0.80 (0.49-1.31)	15/119/180	0.11 (0.01-0.83)	0.56 (0.36-0.88)	0.60 (0.38-0.94)
Triglycerides (mmol/l)							
1.7 or lower	802/236	Ref	Ref	60/460/227	Ref	Ref	Ref
above 1.7	262/121	1.20 (0.86-1.67)	1.28 (0.84-1.95)	21/143/774	2.43 (1.06-5.55)	1.12 (0.76-1.66)	1.01 (0.70-1.47)
HDL cholesterol (mmol/l)							
1.0 or lower	200/71	Ref	Ref	19/95/157	Ref	Ref	Ref
above 1.0	589/280	0.42 (0.30-0.59)	0.44 (0.30-0.67)	41/307/521	0.14 (0.05-0.37)	0.26 (0.18-0.37)	0.67 (0.46-0.96)

3.5: Competing risks analysis

In the competing risks analysis (supplement *table 3*), serum total cholesterol and triglycerides were positively associated with cancer mortality (HR 1.17, CI95% 1.05-1.30 and HR 1.27, CI95% 1.14-1.43, respectively). In contrast, LDL and HDL cholesterol remained inversely associated with cancer mortality similar to the main analysis (HR 0.89, CI95% 0.78-1.02 and HR 0.64, CI95% 0.56-0.74, respectively).

Supplement table 3: Competing risks analysis

Lipid fraction	Competing risks analysis
	HR (95% CI)
n of cancer deaths (non-exposed/ exposed)	858/572
Total cholesterol	
5 or lower	Ref
above 5	1.17 (1.05-1.30)
LDL	
3 or lower	Ref
above 3	0.89 (0.78-1.02)
HDL	
1 or lower	Ref
above 1	0.65 (0.56-0.74)
Triglycerides	
1.7 or lower	Ref
above 1.7	1.27 (1.14-1.43)

4: DISCUSSION

As expected from the results of previous studies, an inverse association between serum total cholesterol and cancer mortality was observed. The association disappeared in long term analysis after 10 years' time lag. However, our comprehensive data of the different lipid components in the long term reveals more about the exact nature of the relationship.

The inverse association between serum cholesterol and all-cancer mortality persisted up to 10 years in our lag time analysis. In analyses with longer time lag the risk estimates for hypercholesterolemia tended to increase, a trend which was observed separately for many individual cancer types. HDL cholesterol showed the strongest inverse association with cancer mortality. Both high HDL and LDL levels were associated with lowered cancer mortality. High

triglyceride levels were generally associated with increased, but not statistically significant risk estimates for cancer mortality.

Previously it has been suggested that the apparent inverse association between serum total cholesterol levels and cancer is attributable to reverse causation due to the association disappearing when excluding the first years of follow-up[7–11]. The time-dependent analyses in our study produced similar results, supporting this hypothesis.

A likely explanation for these findings is the increased lipid uptake by cancer cells. Increased de novo lipogenesis is a well-established trait of cancer metabolism[3]. More recently, however, its' importance has been debated and there has been rising interest in the role of exogenous lipid uptake as well. Hypoxia, a common feature in solid tumors, has been shown to decrease enzyme activity in de novo lipogenesis pathways and simultaneously upregulate lipid uptake[4,24,25]. The phenomenon has been proposed to have a role in metastatic tumor progression[26,27] and might even present a novel therapeutic target[27,28].

We also explored the effect of non-cancer mortality has on the association. In our competing risk analysis, where non-cancer mortality is accounted for, the inverse association turned into a risk increase, driven mainly by risk increase associated with high triglyceride level. For HDL and LDL, the risk decrease remained similar to the main analysis. This analysis, however, is not directly comparable with our main analysis because cholesterol levels could not be analyzed as a time-dependent variable in the competing risks analysis. To produce a more comparable analysis we ran a non-time-dependent cox regression analysis *(supplement table 4)* that produced almost identical results with the competing risks analysis, indicating that the positive association is most likely a result of inability to account for changes in cholesterol levels over time. The effect modification by comorbidities was further explored in the subgroup analysis by Charlson comorbidity index points. The inverse association between HDL cholesterol and cancer mortality was strong among the low comorbidities group and weaker in the group with most comorbidities, demonstrating that competing causes of death tend to attenuate the risk association with cholesterol level rather than increase it. Therefore the risk decrease observed for high total cholesterol is unlikely to be explained by competing causes of death.

Supplement table 4: non-time-dependent cox regression analysis

Lipid fraction	Non-time dependent analysis
	HR (95% CI)
n of cancer deaths (non-exposed/ exposed)	858/572
5 or lower	Ref
above 5	1.17 (1.05-1.30)
LDL	
3 or lower	Ref
above 3	0.80 (0.70-0.91)
HDL	
1 or lower	Ref
above 1	0.54 (0.47-0.62)
Triglycerides	
1.7 or lower	Ref
above 1.7	1.44 (1.29-1.62)

We also studied the association between reduction in cholesterol levels among users of cholesterol-lowering statin drugs and cancer mortality to explore the possibility of serum cholesterol being a modifiable risk factor for cancer mortality. A reduction in cancer mortality has been previously observed among statin-users[21], but the mechanism of action is still somewhat unclear. Both systemic reduction of circulating cholesterol levels as well as local tumor growth inhibitory effects on the cancer tissue have been proposed[29]. In our analysis, statin users whose serum total cholesterol decreased had a lower risk of cancer death compared to those whose cholesterol level did not change, but the risk difference was not statistically significant. Thus, our findings offer modest support for the hypothesis of systemic cholesterol level being a modifiable risk factor for cancer death, albeit our analysis might be lacking statistical power to properly explore the association.

A major strength of our study was the cohort being population-based, reducing the risk of selection bias. We also had data on all lipid fractions, which many of the previous studies lacked. The spontaneous decrease in serum cholesterol levels during cancer progression[6] makes it important to analyze the association on a sufficiently long time span. We had access to several decades of lipid values allowed for analysis of measurements preceding cancer death for up to 20 years. The lipid levels were treated as time-dependent variable in order to model for changes in cholesterol levels during the follow-up. Another strength was comprehensive drug prescription data acquired via national prescription database, making It possible to analyze cholesterol reduction during statin use.

A limitation of our study was that cholesterol measurements were not obtained randomly; the factors leading to cholesterol measurement may introduce selection for certain types of individuals, for instance those with known cardiovascular risk factors or health-conscious people. Another weakness was lack of information on smoking status, exercise and diet, all of which are likely associated both with serum cholesterol levels and cancer mortality.

A possible source of bias is that the number and frequency of cholesterol measurements was not standardized. Likely persons with hypercholesterolemia and/or cardiovascular disease were tested more often, making our data on cholesterol level more precise in this subgroup compared to men with no such problems and possibly only few measurements available as follow-up for cholesterol level was unnecessary. This selection was highlighted in population characteristics; proportion of statin users was higher in men whose mean cholesterol was below 5 mmol/l than in men with elevated cholesterol; such unexpected difference can be caused either by statin usage mainly for secondary prevention of cardiovascular disease irrespective of cholesterol level or because the mean cholesterol is mainly influenced by more numerous cholesterol measurements after statin use when the level has been normalized. When stratified by baseline cholesterol proportion of statin users was higher in the hypercholesterolemic group. However, the number of available measurements did not modify the risk association between cholesterol level and cancer mortality in subgroup analysis. Thus this bias is unlikely to affect our findings to any great degree.

5: Conclusion

Hypercholesterolemia is associated with lowered cancer mortality for up to 10 years before cancer death, supporting reverse causation; i.e. spontaneously lowering cholesterol in people with fatal cancer. The risk association is unlikely to be explained by competing causes of death. Cholesterol-lowering with statins may lower the risk of cancer death, supporting hypercholesterolemia as a modifiable cancer risk factor.

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